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TITLE: Restoring Proprioception via a Cortical Prosthesis: A Novel Learning-Based Approach

PRINCIPAL INVESTIGATOR: Philip Sabes, PhD

CONTRACTING ORGANIZATION: The Regents of the University of California, San Francisco
San Francisco, CA 94103

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Philip Sabes, PhD

E-Mail: sabes@phy.ucsf.edu

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University of California, San Francisco
1855 Folsom St Ste 425
San Francisco CA 94103-4249

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13. SUPPLEMENTARY NOTES

14. ABSTRACT

The goal of this work is to use electrical microstimulation to provide artificial proprioception for individuals using Brain-Machine Interfaces (BMIs), and particular for spinal cord injury. Preliminary results suggest that performance levels with combined artificial feedback and visual feedback exceeds that achievable with visual feedback alone. We have also developed new and powerful schemes to remove the electrical artifacts due to microstimulation from the neural recordings used for BMI control. This allows us to move to a much more efficient paradigm with continuous brain "read out" for BMI control of an external device and "write in" for artificial sensory feedback from that device.

15. SUBJECT TERMS

Spinal cord injury; brain-machine interfaces; artificial feedback; proprioception; somatosensation; microstimulation; movement control

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Table of Contents

1. INTRODUCTION:

Spinal cord injury (SCI) often leads to both the loss of ability to move ones limbs and the loss of sensation from the limbs. One key component of this lost sensation is proprioception, the feeling of where the body is in space. The importance of proprioception is often not appreciated; without it, we are unable to move normally. Even if there were therapies that could restore movement to spinal cord injured patients, without proprioception those movements will be slow, clumsy and uncoordinated. The goal of this work is to restore proprioception for these individuals. In particular, we are focusing on restoring proprioception in the context of brain machine interfaces (BMIs), in which neural activity from the brain's motor centers is monitored and used to guide control of an assistive device such as an orthotic limb. We are working to develop and test a "bi-directional" BMI, which both monitors neural activity in motor areas of the cerebral cortex and delivers artificial proprioceptive feedback via intracortical microstimulation (ICMS) to a somatosensory cortical area. Since these precise neural patterns needed to evoke the correct proprioceptive sense is not known in advance, we are focusing on the brain's ability to learn to interpret new signals. In previous work, we showed that the brain can learn to interpret arbitrary patterns of ICMS activation and can use those patterns to guide movement (Dadarlat, O'Doherty, and Sabes, *Nature Neuroscience*, 2015). We are working to extend this approach to a bi-directional BMI.

2. KEYWORDS:

Spinal cord injury; brain-machine interfaces; artificial feedback; proprioception; somatosensation; microstimulation; movement control

3. ACCOMPLISHMENTS:

What were the major goals of the project?

<u>Specific Aim 1: Determine whether animals can learn to use artificial proprioception</u>

Artificial proprioception is delivered The ICMS feedback signal will not at first be meaningful to the animals. However, that signal will correlate on a millisecond timescale with visual feedback of the virtual limb. Based on the previous work (Dadarlat et al., 2015), we expect these correlations to drive naturalistic integration of ICMS. After learning, we will use behavioral measures to determine how well the animal can interpret the ICMS signal, alone and combination with visual feedback. We will determine whether ICMS and vision are integrated in a minimum-variance manner, as expected for "natural" sensory signals.

- Major Task 1.1: Train animals in basic procedures (Months 1-6)
  - This task is complete.
- Major Task 1.2: Experiment 1 – data collection (Months 1-13)
  - <u>Monkey 1</u>: In our first experiment with Monkey 1, we had found that the animal's performance with artificial proprioception (delivered via ICMS) and vision was improving, compared to that achieved with vision alone. The pace of learning was comparable to our earlier published study. However, as reported at the time, we encountered a technical setback: the electrode array in M1 of Monkey 1 failed, no longer providing robust enough single unit recordings to provide high-quality BMI control. We therefore had to explant the arrays in this animal.

    While we waited for the animal to recover, we conducted two sets of ancillary experiments which led to large improvements in our approach. First, we have developed and

successfully demonstrated the first system for stimulation artifact removal in a closed-loop system high-pulse-rate, multi-electrode stimulation. Second, we have developed the first approach to measuring the rate of task-relevant information received by a performed from a sensory feedback stream; we will use this quantify the performance of our artificial proprioception. These developments, described in more detail below, can both generalize to other efforts aimed at artificial sensory feedback.

  The main experiment has once again commenced, using these improvements (details below).

  - Monkey 2: The second animal has been trained on the basic behavioral tasks and we are currently collecting data from that animal for the information rate measurement study. We will implant arrays in this animal in January 2017.

- Major Task 1.3: Experiment 1 – data analysis (Months 4-22)
  - We have made considerable progress on data analysis, including the two advances described below. Details are given below.

Specific Aim 2: Determine whether artificial proprioception improves BMI learning rate and asymptotic performance

Whether or not naturalistic integration is achieved in Aim 1, we expect that the addition of feedback signals directly to S1 will improve BMI performance. We will measure the learning rate for a new BMI controller, the asymptotic performance of that controller, and the long-term stability of control, and compare these measures for cases with and without artificial proprioceptive feedback.

- Major Task 2.1: Experiment 2 – data collection (Months 10-30)
  - The start of these experiments has been delayed due to delays in Major Task 1.2. We still expect to be able to accomplish the key elements of this experiment by the end of the funding period. In particular, we will able to measure asymptotic performance with and without artificial proprioception with the current experiment.
- Major Task 2.2: Experiment 2 – data analysis (Months 12-36)
  - This task will begin shortly after the start of Experiment 2.

What was accomplished under these goals?

Major Tasks 1.2-1.3: Stimulation Artifact Removal. As noted in previous reports, a key challenge for closed-loop BMI systems like the one we are developing here is that large-scale, high-bandwidth electrical micro-stimulation of the brain will lead to very large stimulation artifacts (SA). We have reported on new techniques for SA removal that are robust to stimulation site, and should therefore work with multisite stimulation, as required for this project. This allows us to stimulate complex patterns across 16 independent simulating electrode-pairs in primary somatosensory cortex (S1) while recording SA-free action potentials on a full 96-electrode array in motor cortex (M1). The final implementation of this system, which are using for experiment 1, has several components to it:

1. SA minimization:
   a. Bipolar stimulation: We find that the SA is about 2-5x small when we stimulate with bipolar current (i.e., between two electrodes that alternate as anode and cathode) versus monopolar stimulation (i.e., through a single electrode with a distant ground).
   b. Pulse queuing: The SA removal pipeline described below can remove SA on when as many as 3-5 simultaneous pulses are delivered. Above that number, the amplifiers

sometimes clip. To be safe, we have therefore limited ourselves to three simultaneous pulses. However, with high stimulation rates (up to 200Hz) across 16 electrodes (as required in our experiment, see below), there are often more than three pulses that would overlap. Therefore, we use a pulse-scheduling scheme, in which pulses are delivered on a 2 or 3 ms clock. If >3 pulses would occur on a given cycle, only the first three are delivered, and the rest are pushed onto a FIFO queue to be delivered in subsequent cycles. In practice, we have shown that this leads to minimal distortion in the pulse rate pattern across electrodes.

2. SA removal:
    a. Mean SA subtraction: We measure the mean SA on each electrode and subtract that from the raw signal. This removes much of the artifact
    b. Regression-based SA removal: We then use a regression-based scheme. For each recording electrode, we use linear regression to predict the signal on that electrode from the remaining recording electrodes. This prediction captures the residual SA without changing the high-frequency signal that contains action potentials.

This complete pipeline is highly effective, as demonstrated in Figure 1, which shows very good artifact rejection for each of 4-choose-8 sets of the 4 electrodes used for position coding, and in Figure 7, below, which shows the complete closed-loop system for Experiment 1.

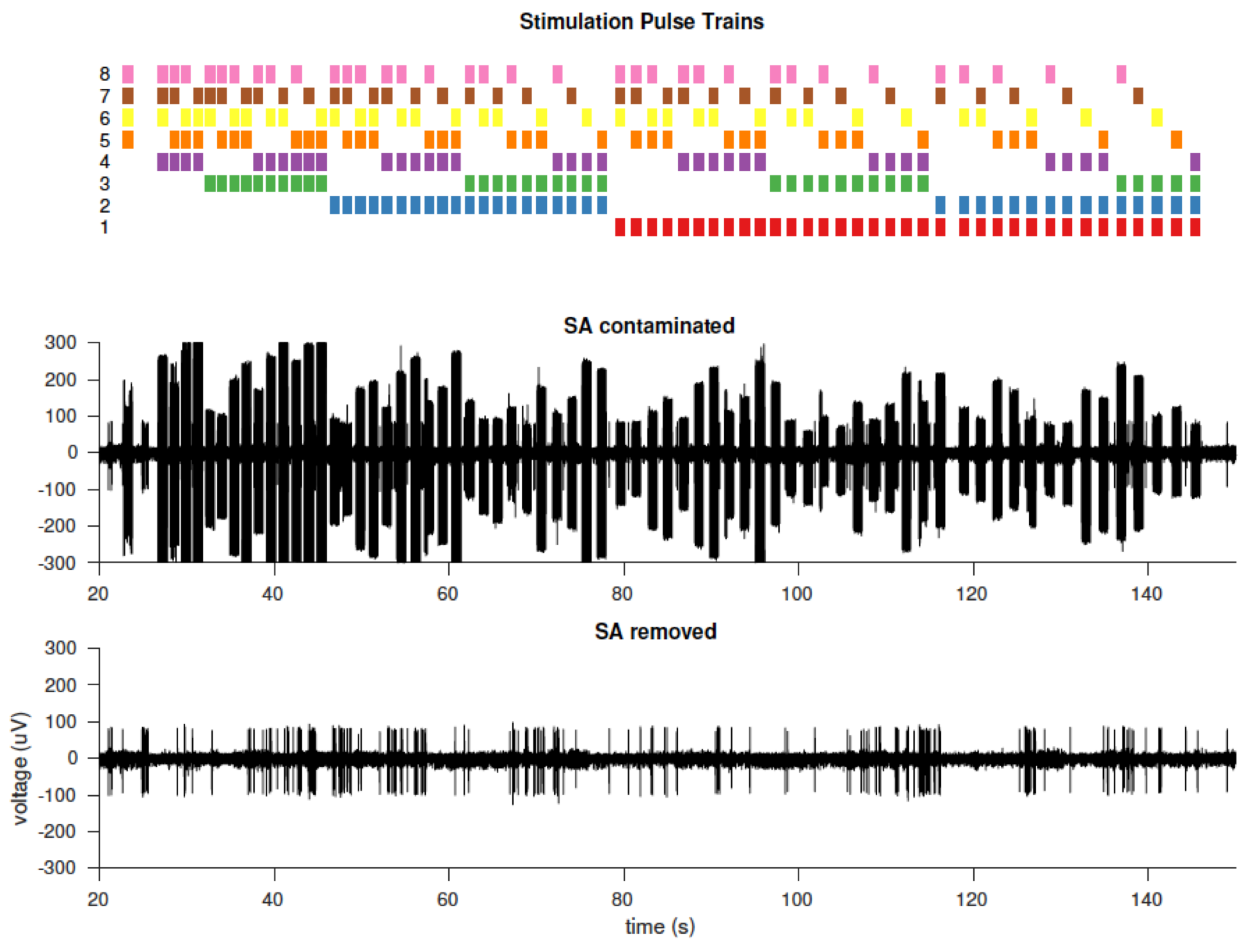


Figure 1. Each plot shows an FFT spectrum of neural activity recorded from the M1 array. Spectra are shown for raw data (black line on the left, no stimulation; pink line on the right, during stimulation) and for artifact subtracted data (blue lines), using each of the two algorithms. The left plot shows how each SA removal method effect true physiologial signal; the right plot shows that both methods are good at removing the SA (note the log scale).

Major Tasks 1.2-1.3: Measuring Feedback Information Rate. The principle goal of this work is to deliver artificial proprioception using ICMS. A key challenge that faces this effort is that of quantifying the degree of performance improvement that the artificial provides. In particular, adequate methods are lacking for quantifying the information rate of sensory feedback modalities for the execution of movements.

To address this gap, we have employed a critical stability task (CST) to quantify closed-loop sensorimotor performance (Quick, Card, Whaite, Mischel, Loughlin, & Batista, 2014). The CST requires subjects to control, moment by moment, the state of an unstable dynamical system using one or more feedback modalities. The index of performance is the maximum level of instability at which the user is able to control the system.

Since this task is highly dependent on the quality of the sensory feedback, we hypothesized that task performance could serve as a good proxy for the task-relevant information rate of the sensory feedback. We realized that this idea could be tested using degraded visual feedback, and that if it worked, we could then use performance with artificial feedback to infer its information rate.

We experimentally manipulated the visual feedback, both to diminish its reliability and to allow for the delivery of quantifiable rates of information. Specifically, we discretized the visual feedback in both time and space (Figure 2). Using this feedback scheme, we collected pilot data with human and macaque subjects and found that CST performance depends on the only on the information rate of the signal, validating the approach (Figure 3, next page). The functional dependence is well modeled by a sigmoid, with a peak inflection at about 15 bit/s. We also tested the performance of Monkey 1 on this task, and found quantitatively similar results.

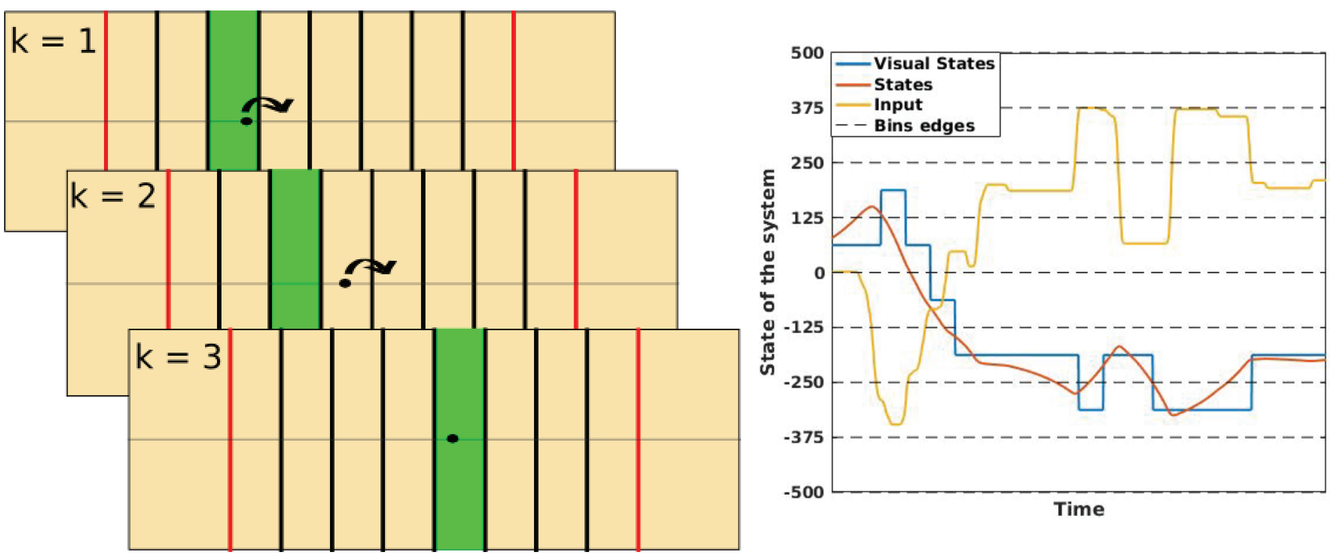


Figure 2: Example of the Discretization in Time and Space on Critical Stability task (left figure). The visual state space of the system is cut in compartments. The red lines are the limits at which we consider that the user failed to stabilize the system. The state of the system is displayed in green while its real state (black dot) is kept hidden from the user. While the system hidden state updates at each step (frequency f), the visual state updates at a different frequency (here f/2). The figure on the right shows the states, the visual states and the input of the system with 8 bins and with a visual frequency update of 2 Hz.

Next, since the Critical stability task is a simple unstable dynamical system, it is possible to build a model that represents the human behavior and maintain the system stable. By modeling the state estimation of the discretized feedback with a Kalman Filter and control with a (feedback-independent) Linear Quadratic regulator, we were able to fit the dependence of human and non-human primate performance on feedback information rate (Figure 4, next page). The match between model performance and empirical data further validates our interpretation as CST performance as a valid proxy for feedback information rate.

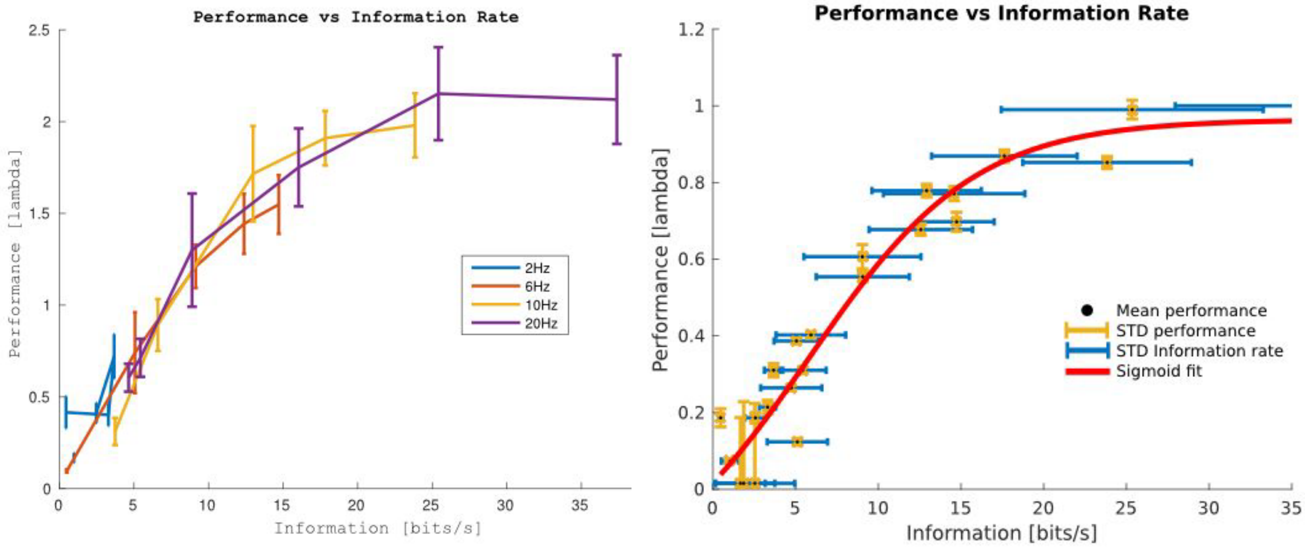


Figure 3: **Left**: Relation between information rate and performance using the transition probability of the system being in one discretized state knowing that it was in a specific state before. The information rate has been computed at different frequencies and number of bins: each point is a specific number of bins and each line is the display update frequency. **Right**: Performance of Monkey 1 at different frequencies and number of bins (difference information rate). Performance, normalized by subject, is modeled with a sigmoid function (R^2=0.86).

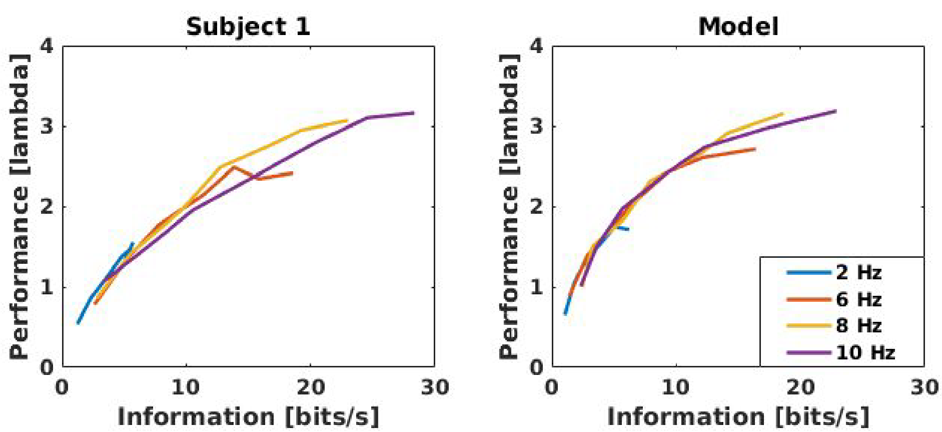


Figure 4: Left. Relation between performance and information rate for a subject at different discretizations in time and space. **Right.** Same relationship obtained with a tuned Kalman filter coupled to a LQR to fit the performance of the corresponding subject.

<u>Major Tasks 1.2-1.3: Principle Experiment 1</u>

We have now restarted the main experiment, in which S1 ICMS is used to provide artificial proprioception from a two-dimensional cursor the animal is controlling via BMI from M1 spiking activity. We are now using an enhanced feedback scheme that delivers information about the both the position and velocity of the feedback. In particular, we are using 16 electrodes, 8 that encode position and 8 that encode velocity. This is change brings the artificial feedback more in line with natural proprioception, which includes both signals. Figures 5-6 illustrate this revised feedback scheme.

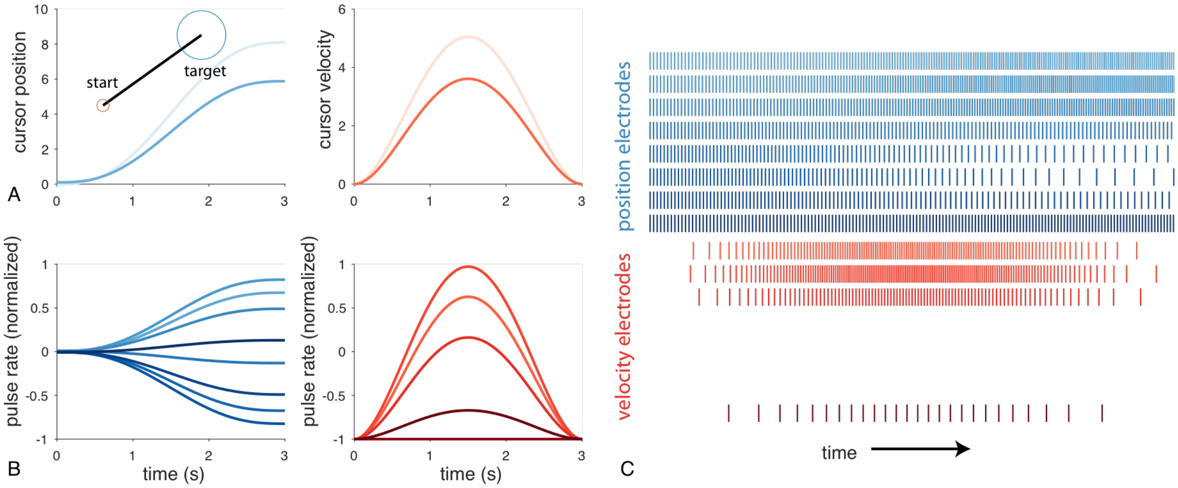


Figure 5. Stimualtion encoding of artificial feedback fro a sample BMI movement trajectory. A) Sample BMI movement trajectory. Plots show position and velocity (x and y) vs. time. The inset shows the straight-line path. B) Pulse rate (mean subtracted and normalized to unit peak) vs. time. The 8 position electrodes are in blue, and the 8 velocity electrodes are in red. Note that four of the velocity electrodes have zero rate. C) Pulse trains for the example trajectory in A.

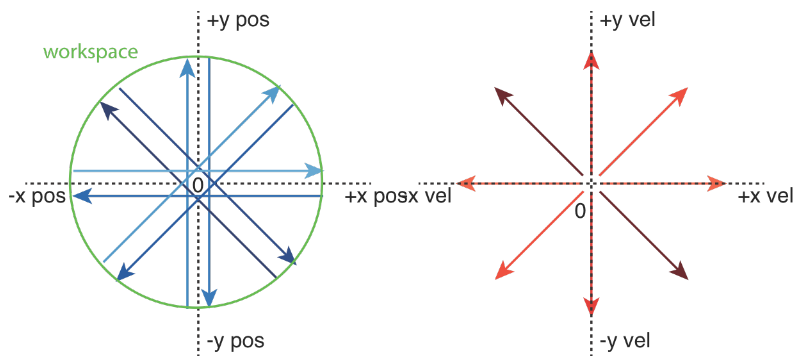


Figure 6. Preferred vectors for the 16 stimulation electrodes. The origin of the eight position electrodes (in blue) are at the edge of the workspace, so that position electrodes are continuously pulsing when the cursor is active. The origin of the velocity electrodes is at zero speed, so that the velocity electrodes are inactive when the animal is not moving (as in Fig. 3B,C).

Using the scheme described above, we are now able to deliver this 16-channel feedback without stimulus artifact, as shown in the included video and in the accompanying Figure 7 below.

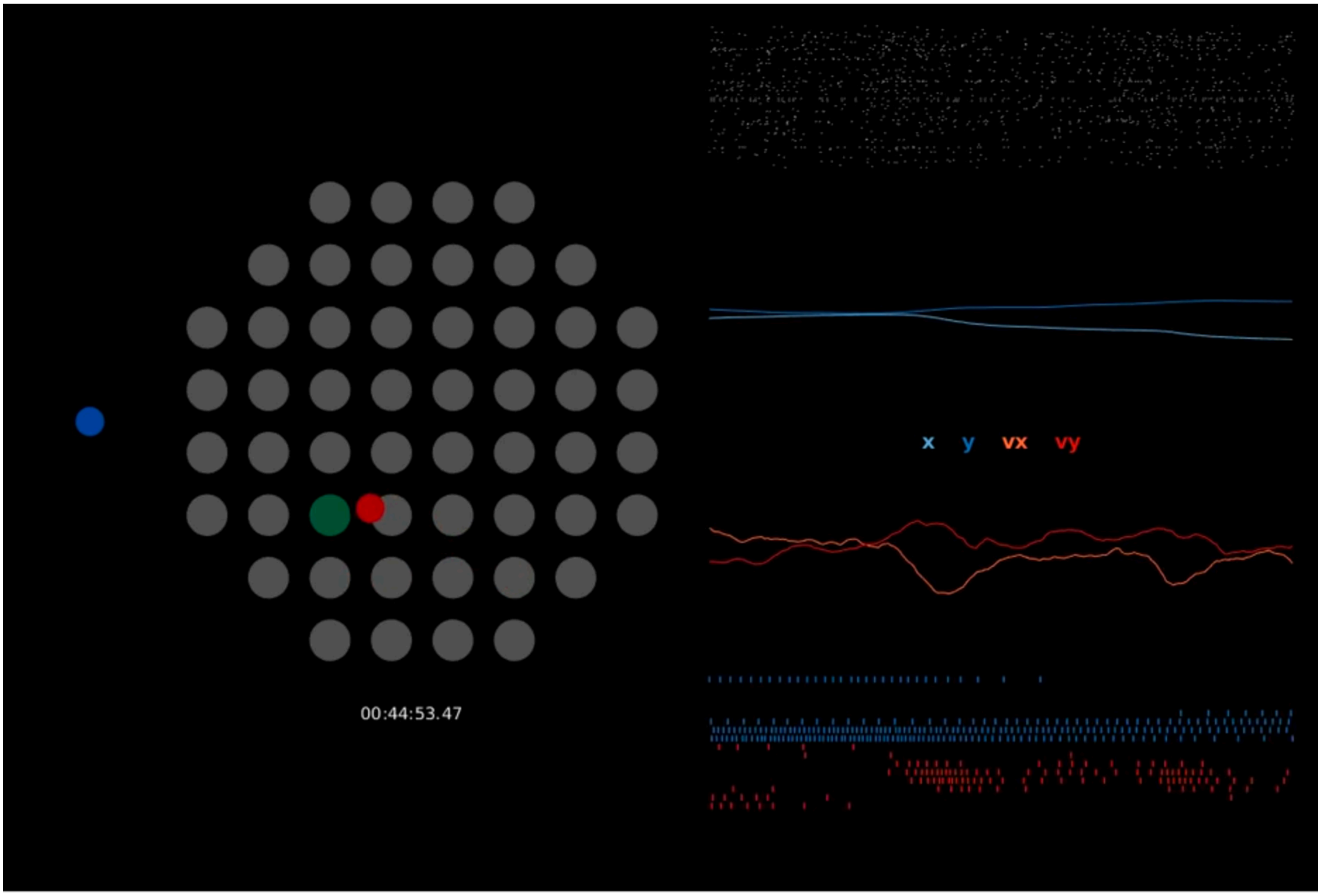


Figure 7. Still image from the included video showing closed-loop BMI. **Left:** The image on the left is what the monkey sees: the set of potential targets (gray circles), the current target (red circle), the BMI-controlled cursor (red circle), and the position of the limb (blue circle, not shown to monkey). Note that the actual limb must remain stationary during the task in order to avoid “cheating” by giving proprioception via the moving hand. **Right:** Closed loop control. The rasters on the top show spike times on each of the recording channels; this is the M1 signal used for BMI control. The traces in the middle show the position (blues) and velocity (reds) of the BMI-controlled cursor. Note that the red velocity traces are decoded directly from the M1 spiking activity. Lastly, the position and velocity are delivered back to the animal via S1 ICMS, with the pulse trains shown at the bottom: blue pulses on electrode pairs representing position, and red pulses on electrode pairs representing velocity.

What opportunities for training and professional development has the project provided?

We hosted a visiting masters student from EPFL (Lausanne, Switzerland) who started the CST-task project described above. He successfully defended his masters thesis on this work, and has returned as an academic specialist to help complete the project. In January, he will be returning to EPFL for his PhD studies.

Based on the success of this effort, we have now brought a second visiting student from Grenoble, France.

How were the results disseminated to communities of interest?

We presented the CST and closed-loop BMI components of this work at the 2016 Society for Neuroscience Meeting.

Two papers are currently in preparation: one on the CST task and its use for measuring the information rate of sensory feedback, and another on our pipeline for SA removal with multielectrode stimulation.

What do you plan to do during the next reporting period to accomplish the goals?

Our effort in the next year will be focused on:

- Major Task 1.2 and 1.3
    - Implanting Monkeys 2
    - Completing Experiment 1 with both monkeys, using the improvements described above, in order to demonstrate improved asymptotic performance with artificial feedgback
    - Publishing several articles:
        - The CST task and its use for artificial feedback
        - Our pipeline for stimulation artifact rejection
        - The learning approach to artificial proprioception
- Major Task 2.1 and 2.2
    - Starting Experiment 2, after completion of data collection for Experiment 1

4. IMPACT:

What was the impact on the development of the principal discipline(s) of the project?

- We have developed powerful new tools for removing artifacts from electrical recordings from the brain due to multielectrode brain microstimulation. We anticipate that these tools will be widely used in the field and will have a substantial impact on the improvement of bi-directional BMIs, i.e. devices that combine neural stimulation and recording.
- We have developed a novel tool for measuring the information rate of an arbitrary sensorimotor feedback stream. This will also be widely useful in the field for both comparing different artificial feedback schemes and for optimizing a given approach.
- Our preliminary results suggest that the use of artificial sensory feedback delivered via brain microstimulation will improve performance of a BMI, compared to performance with visual feedback alone. If these results are replicated and expanded in upcoming experiments, we believe the impact for the BMI community will be great. In particular, this work would show that it is possible to obtain performance benefits even when it is not possible to be able to replicate the patterns of activity that would have occurred before spinal cord injury.

What was the impact on other disciplines?

- The artifact removal scheme will have impact beyond BMI applications. For example, the scheme will be useful for “causal” neuroscience experiments, in which stimulation is used to study the dynamics of brain circuits.
- Our use of the CST, including the modeling of human and macaque performance, will be useful for basic scientific studies of natural feedback-driving closed-loop control.

What was the impact on technology transfer?

Nothing to report

What was the impact on society beyond science and technology?

Nothing to report

5. CHANGES/PROBLEMS:

Changes in approach and reasons for change

Nothing to report

Actual or anticipated problems or delays and actions or plans to resolve them

As reported in previous reports, we experienced delays due the failure of the electrode implants in Monkey 1. We are now back on track and have been training Monkey 1 with closed-loop control for several weeks. We have not yet seen behavioral improvements when comparing conditions with ICMS and vision, compared to vision alone. However, consistent with our earlier published results, we recognize that we may not see improvements with ICMS when visual feedback is highly reliable. Therefore, we will next begin to test performance with and without ICMS in conditions with degraded feedback (as we have previously reported).

Changes that had a significant impact on expenditures

Nothing to report.

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents

Significant changes in use or care of human subjects

Nothing to report (not applicable)

Significant changes in use or care of vertebrate animals.

Nothing to report

Significant changes in use of biohazards and/or select agents

Nothing to report

6. PRODUCTS:

Publications, conference papers, and presentations

We have presented this work in a talk and a poster at the 2016 Society for Neuroscience Meeting (November 2016, San Deigo):

J. O'Doherty and P.N. Sabes, "Towards artificial proprioception for brain-machine interfaces" (Talk 288.08).

J. Rechenmann J. O'Doherty, and P.N. Sabes, "Quantifying the information rate of sensory feedback for

neuroprotheses” (Poster 334.16).

Website(s) or other Internet site(s)

Nothing to report

Technologies or techniques

As described above, we have developed powerful new tools for removing artifacts from electrical recordings from the brain due to simultaneous brain microstimulation and for quantifying the information rate of an artificial feedback scheme. We expect that these tools will find wide application. We are currently preparing manuscripts describing these tools. These manuscripts will provide sufficient information for other groups to readily employ these techniques.

Inventions, patent applications, and/or licenses

Nothing to report

Other Products

Nothing to report

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?
Provide the following information for: (1) PDs/PIs; and (2) each person who has worked at least one person month per year on the project during the reporting period, regardless of the source of compensation (a person month equals approximately 160 hours of effort). If information is unchanged from a previous submission, provide the name only and indicate "no change."

Name:	Philip Sabes, PhD
Project Role:	Principal Investigator
Researcher Identifier (e.g. ORCID ID):	orcid.org/0000-0001-8397-6225
Nearest person month worked:	3
Contribution to Project:	Dr. Sabes is the PI. He has provided supervision and leadership for all aspects of the project
Funding Support:	1. DARPA/Case Western, iSens: Implanted somatosenso electrical neurostimulation 2. DARPA, Unlearning neural systems dysfunction in neuropsychiatric disorders 3. DARPA, A new, scalable approach to high-bandwidth, minimally invasive neural recording and stimulation
Name:	Joseph O’Doherty
Project Role:	Postdoc
Researcher Identifier (e.g.	orcid.org/0000-0001-8175-5699

ORCID ID):	
Nearest person month worked:	12
Contribution to Project:	Dr. O'Doherty has been principally responsible for performing the experiments and analyses in this project.
Funding Support:	
Name:	Lindsey Presson
Project Role:	Staff Research Assoc/Animal Health Tech.
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	6
Contribution to Project:	Ms. Presson has overseen basic animal care and traning, as well as lab management and regulatory oversight
Funding Support:	
Name:	Julien Rechenmann
Project Role:	Junior Academic Specialist
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	3
Contribution to Project:	Mr. Rechenmann has led the CST project (measuring feedback information rate) and has taken responsibility fo training Monkey 2
Funding Support:	

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?

<u>No change</u>

What other organizations were involved as partners?

Nothing to report

8. SPECIAL REPORTING REQUIREMENTS

See attached Quad Chart.

9. APPENDICES:

Video included - O'DohertySabes_ClosedLoopControlDemo.m4v

Restoring Proprioception via a Cortical Prosthesis: A Novel Learning-Based Approach

SC130074

W81XWH-14-1-0510

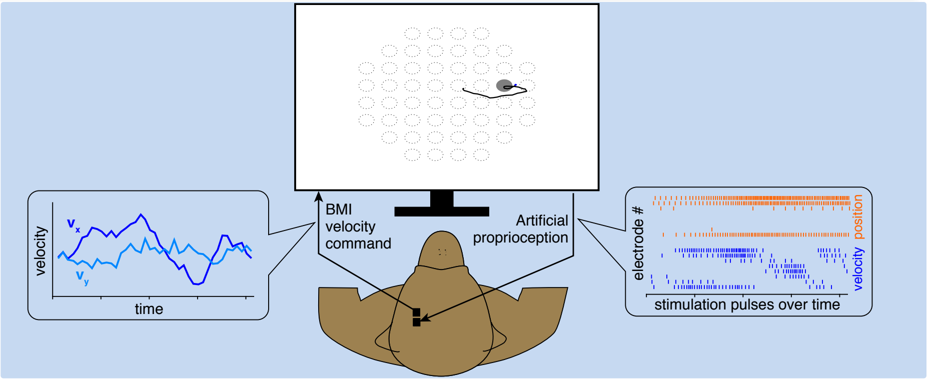
PI: Philip N. Sabes **Org:** UCSF **Award Amount:** $710,683

Study/Product Aim(s)

- Determine whether animals can learn to use artificial proprioception delivered via intracortical microstimulation (ICMS) to primary somatosensory cortex
- Determine whether artificial proprioception improves brain-machine interface (BMI) learning rate and asymptotic performance

Approach

A key factor that has limited performance of neuroprostheses is the lack of natural proprioceptive feedback. Our objective is to develop a learning-based approach for providing artificial proprioception, taking advantage of the brain's capacity for plastic reorganization.



Example of true closed-loop BMI. Neural activity from motor cortex of Monkey 1 is decoded into intended cursor velocity. Artificial feedback encoding both cursor position and velocity is delivered to somatosensory cortex via 16 channels of intracortical microstimulation (ICMS).

Timeline and Cost

Activities CY	14	15	16	17
1.1: Train animals in basic procedures				
1.2: Expt. 1 – artificial feedback with learned BMI control: data collection				
1.3: Expt. 1 –data analysis				
1.2: Expt. 2 – artificial feedback while learning BMI control: data collection				
1.3: Expt. 2 –data analysis				
Estimated Budget ($K)	**$55**	**$189**	**$257**	**$211**

Updated: 28 November 2016

Goals/Milestones

CY14 Goal – Behavioral Training

☑ Preliminary, basic behavioral training

CY15 Goals – Demonstrate artificial feedback with learned BMI

☑ Perform Experiment 1

CY16 Goal – Begin simultaneous learning of artificial feedback and BMI

☐ Complete Experiment 1 and prepare manuscript

☐ Perform Experiment 2

CY17 Goal – Obtain improved learning and performance with feedback

☐ Complete Experiment 1 and prepare manuscript

Comments/Challenges/Issues/Concerns

- Need to re-implant Monkey 1, but artifact rejection will make for a more efficient closed-loop control scheme

Budget Expenditure to Date

Projected Expenditure: $435,931

Actual Expenditure: $431,545